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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/666,152	09/20/2000	Kimiyuki Shibuya	49218-C	7703
21874	7590	12/10/2003	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 9169 BOSTON, MA 02209			STOCKTON, LAURA LYNNE	
			ART UNIT	PAPER NUMBER
			1626	

DATE MAILED: 12/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/666,152	<b>Applicant(s)</b> SHIBUYA ET AL.	
	<b>Examiner</b> Laura L. Stockton, Ph.D.	<b>Art Unit</b> 1626	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 November 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 9-12 and 14-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 15-18 is/are allowed.
- 6) ☒ Claim(s) 9-12 and 14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
     a) ☐ All    b) ☐ Some \*    c) ☐ None of:  
         1. ☐ Certified copies of the priority documents have been received.  
         2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
         3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
     \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
     a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>09/18/2003</u> | 6) <input type="checkbox"/> Other: _____                                    |

## DETAILED ACTION

Claims 9-12 and 14-18 are pending in the application.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on September 16, 2003 has been entered.

Rejections made in the previous Office Action that do not appear below have been overcome. Therefore, arguments pertaining to these rejections will not be addressed.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 9-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable Hirai et al. {JP 04-139172}. An English translation of Hirai et al. has been supplied previously.

*Determination of the scope and content of the prior art (MPEP §2141.01)*

Applicants claim benzoxazole compounds. Hirai et al. teach benzoxazole compounds which are structurally similar to the instant claimed compounds. See in Hirai et al., for example, wherein R<sup>1</sup>-R<sup>4</sup> are each hydrogen, A is oxygen, R<sup>5</sup> is alkyl, and R<sup>6</sup> is a substituted heteroaryl group (pages 1 and 2 of the Japanese patent and pages 6 and 16 of the English translation). Also see, for example, compounds 5, 9, 17, 18, 34, 71, 72 and 77 in the Table on pages 7 and 8 of the Japanese patent.

*Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)*

The difference between the compounds in the prior art and the compounds instantly claimed is that of positional isomerism (the instant  $n$  is 2 whereas  $R^5$  is methyl in the prior art and the  $-C(O)NHR^6$  group is attached to the fixed carbon,  $-CHR^5$ ). In other words, the instant claimed compounds, for example, have an “ethylene” group  $\{-CH_2CH_2-\}$  whereas the prior art teaches an “ethylidenyl” group  $\{-CH(CH_3)-\}$ .

Alternatively, the difference between the compounds in the prior art and the compounds instantly claimed is that Applicants are claiming a homolog of the compounds taught in the prior art (the instant  $n$  is 2 whereas  $R^5$  is hydrogen in the prior art and the  $-C(O)NHR^6$  group is attached to the fixed carbon,  $-CHR^5$ ). In other words, the instant claimed compounds, for example, have an “ethylene” group  $\{-CH_2CH_2-\}$  whereas the prior art teaches a “methylene” group  $\{-CH_2-\}$ .

*Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)*

Nothing unobvious is seen in substituting the known claimed isomer for the structurally similar isomer, as taught by Hirai et al., since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. In re Norris, 84 USPQ 458 (1950).

Alternatively, to those skilled in chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. In re Henze, 85 USPQ 261 (1950).

One skilled in the art would have been motivated to prepare positional isomers or homologs of the compounds in the prior art to arrive at the instant claimed compounds with the expectation of obtaining additional beneficial compounds that would be useful in treating ulcers. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

*Response to Arguments*

Applicants' arguments filed September 16, 2003 have been fully considered. Applicants argue that the instant claimed compounds are structurally different from those disclosed in Hirai et al. Applicants argue that all of the compounds disclosed in Hirai et al. have a methylene linker (or a 1,1-ethanediyl linker), which may be substituted, linking the amide residue and the 2-oxo-benzoxazole or 2-sulfanyl-benzoxazole residue. Applicants argue that, in contrast, the present invention provides compounds of Formulas I, IA and III where the linker between the benzoxazole residue and the N-aryl amide (e.g., -C(O)NHAr) comprises at least a two carbon diradical (e.g., 1,2-ethylene or a  $\alpha,\omega$ -alkylene group). Applicants argue the importance of the linking group between the benzoxazole group and the amide group and cites reviews by Brandstrom et al. and Lindberg et al. of a structure-activity relationship (SAR) study conducted for Omeprazole and related compounds. Applicants argue that the structure of Omeprazole is similar to the compounds of Hirai et al. Therefore, Applicants conclude from SAR

study of Omeprazole that the compounds of Hirai are unable to exhibit  $H^+$ ,  $K^+$ -ATPase inhibitory activity.

All of Applicants' arguments have been considered but have not been found persuasive. Applicants claim benzoxazole compounds. Hirai et al. teach benzoxazole compounds which are structurally similar to the instant claimed products. See pages 1 and 2 of the Japanese patent and pages 6 and 16 of the English translation. Also see, for example, compounds 5, 9, 17, 18, 34, 71, 72 and 77 in the Table on pages 7 and 8 of the Japanese patent. The instant claimed products are homologs or positional isomers of the compounds taught in the prior art. To those skilled in chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members.

The instant specification, under the heading "Best Mode For Carrying Out the Invention" {pages 12-13 (n is 1 to 15)} and the originally filed claims {e.g., claim 1, page 232 (n is 1 to 15)} support the



expectation that homologs would have similar activity. The instant disclosed invention teaches that the instant compounds have ACAT inhibiting activity:

when **n is 1** (e.g., a **methylene** linker linking the amide residue and the 2-sulfoxide-benzoxazole residue) or

when **n is 2** (e.g., an **ethylene** linker linking the amide residue and the 2-sulfoxide-benzoxazole residue).

Also, see Compound Numbers 1-10 on page 32 of the instant specification. One skilled in the art would expect homologs to have similar activity as does Applicants as shown by the **n** variable being defined as 1 to 15 under the heading "Best Mode For Carrying Out the Invention" and by the specific disclosed specie.

Additionally, it is not agreed upon that the structure of Omeprazole is similar in structure to the compounds of Hirai et al. The compounds of Hirai et al. have an amide group (as does Applicants' compounds) whereas Omeprazole does not have an amide group. Also, Omeprazole has a benzimidazole ring and not a benzoxazole ring (as is instantly

claimed). Therefore, the showings in Brandstrom et al. and Lindberg et al. are not sufficient to overcome a rejection of the claims under 35 USC § 103. Applicant relying upon comparative showing to rebut a *prima facie* case must compare his claimed invention with the closest prior art.

Absent factual evidence of unexpected, beneficial and superior results of the instant claimed compounds over the prior art, the instant claimed compounds are obvious over the prior art. For all the reasons given above, the rejection of the claims is proper and is maintained.

#### ***Allowable Subject Matter***

Claims 15-18 are allowed over the art of record.

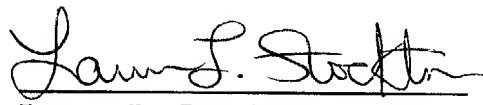
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (703) 308-1875. The examiner can normally be reached on Monday-Friday from 6:00 am to 2:30 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (703) 308-4537.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

A handwritten signature in cursive script, reading "Laura L. Stockton", written over a horizontal line.

Laura L. Stockton, Ph.D.

Patent Examiner

Art Unit 1626, Group 1620

Technology Center 1600

December 8, 2003